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Copy Number Variants and Therapeutic Response to Antidepressant Medication in Major Depressive Disorder

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Disclosures

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Abstract

Objective: It would be beneficial to find genetic predictors of antidepressant response to help personalise treatment of major depressive disorder (MDD). Rare copy number variants (CNVs) have been implicated in several psychiatric disorders including MDD, but their role in antidepressant response is yet to be investigated.

Methods: CNVs were assessed using genome wide microarrays in 1565 individuals from the NEWMEDS consortium where we had prospective data on outcome of treatment of MDD with either a serotonergic or noradrenergic antidepressant for up to 12 weeks.

Results: We found no association between presence of rare CNVs, number of CNVs or CNV 'burden' and antidepressant response, response to serotonergic antidepressants, response to noradrenergic antidepressant or differential response to serotonergic versus noradrenergic antidepressants. Neither was there a relationship between antidepressant response and common CNVs.

Conclusions: Together with similarly negative data for common genetic variants, our present findings imply that personalising treatment with antidepressants based on genetic information will be a more complex task than had hitherto been expected.

Introduction:

Antidepressants are the first line of treatment for major depressive disorder (MDD). However individuals vary widely in their response to treatment and currently there is no way to predict an individual's response. Prediction of how an individual will respond to a specific treatment is needed to reduce the delay to alleviation of symptoms and the cost of treatment and disability. While the existence of any single common genetic variant with a large enough effect to meaningfully predict antidepressant response is unlikely (1-5) we have shown that antidepressant response is moderately heritable (Tansey et at BP paper) and other forms of genetic variation remain to be investigated for a role in antidepressant response.

Copy number variants (CNVs) are submicroscopic deletions and duplications in genomic DNA that have been implicated in a variety of different psychiatric disorders including schizophrenia, autism, ADHD and MDD (6-12). Individuals with MDD have been shown to have an increased burden of rare deleterious CNVs compared to controls (12). We hypothesise that rare deleterious CNVs may also affect how individuals respond to treatment with antidepressants. To date, there is no published report on the relationship between CNVs and response to treatment with antidepressants. In this manuscript, we use information from Illumina genotyping arrays to assess the role of CNVs in response to treatment with antidepressants in individuals with MDD.

Materials and Methods:

Sample

The Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS)(http://www.newmeds-europe.com) sample included 2,146 treatment seeking adults diagnosed with MDD according to DSM-IV/ICD-10, with prospective data on outcome of treatment with SRI or NRI antidepressants for up to 12 weeks (1). This sample

combined data from studies conducted by academic institutions (GENDEP, n=868; GENPOD, n=601; GODS, n=131) (2, 13, 14) and pharmaceutical industry members of the European Federation of Pharmaceutical Industries and Associations (EFPIA; Pfizer, n=355; GSK, n=191). Individuals were excluded if they had diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder or current alcohol or drug dependence. Individuals were given either an antidepressant that acts primarily through blocking the reuptake of serotonin (SSRI: escitalopram, citalopram, paroxetine, sertraline, fluoxetine) or an antidepressant that acts primarily through blocking the reuptake of norepinephrine (NRI: nortriptyline, reboxetine).

Further information on the component studies can be found in Supplementary materials.

Genotyping

All DNA samples were from venous blood. Information was available from 1,166 samples genotyped on the Illumina 660W BeadChip and 746 samples genotyped on the Illumina 610Quad BeadChip (Illumina, San Diego, USA), which have identical tag SNP coverage. Raw Illumina data in the form of .idat files were imported into GenomeStudio and processed according to Illumina's recommended guidelines to derive the log R ratio (LRR) and B allele frequency (BAF) for each marker within each sample. A consensus marker set between the Ilumina arrays of 561,733 markers was used.

CNV Calling

LRR and BAF data was processed with PennCNV (15) (version dated June 2011) and QuantiSNP (16) (version 2.3) using all markers and within-sample correction for waviness artefacts attributable to local GC content. The 'HD' prior parameter settings for LRR thresholds were used within the QuantiSNP analysis, as recommended by the author.

Due to variability between calling algorithms, we used two CNV calling algorithms (PennCNV and QuantiSNP) to minimize the number of false calls. A recent study showed the use of multiple calling algorithms increases the likelihood of validation by PCR to greater than 95% (17). CNV calls were merged between PennCNV and QuantiSNP. Specifically, a call or calls made by QuantiSNP or PennCNV were merged into a consensus call if, within the same sample, the calls overlapped. Only calls with overlap of greater than 50% between the two regions were used for onward analysis. We excluded any call made with less than 10 consecutive markers, and any CNV where 50% of the call covered a region within 500kb of the telomere, centromere or immunoglobulin regions, or a region where the marker density of the consensus marker set dropped below one marker in 200,000bp.

Sample and CNV Quality Control

Sample QC was performed using sample-wide metrics calculated by PennCNV. A sample was excluded from further analysis if any of the following criteria were met: (A) the standard deviation of the LRR for autosomes was greater than 0.25, (B) the standard deviation for the BAF for autosomes was greater than 0.04, (C) the drift of BAF values exceeded 0.002, (D) the waviness factor was greater than 0.04 or less than -0.04, (E) the genotype call rate was less than 98%, (F) the logarithm of the total number of CNVs called by either algorithm before CNV call QC and after samples were excluded by steps A-E exceeded three standard deviations from the mean.

Only samples which passed quality control for our whole genome association study were considered for the analysis of CNVs. This ensured that individuals with ambiguous sex (n=22), abnormal heterozygosity (n=16), cryptic relatedness up to third-degree relatives by identity by descent (n=20), and non-European ethnicity admixture detected as outliers in an iterative EIGENSTRAT analysis of an LD-pruned dataset (n=35) (1) did not impact on the association results.

Definition of Antidepressant Response Phenotype

We defined antidepressant response as a proportional reduction in symptoms over the course of treatment, consistent with previous reports (1, 2). Proportional improvement in depression severity was created for each component study based on the primary depression rating scale from baseline to the end of treatment, adjusted for age, sex and recruiting centre. Depression severity was measured by one of three primary rating scales (Montgomery-Åsberg Depression Rating Scale, Hamilton Rating Scale for Depression, Beck Depression Inventory) (18). The adjusted change score for each component study was z-transformed within each study to remove correlation between data origin and outcome and to eliminate study specific effects.

Statistical Analysis

Statistical analyses were done using PLINK (19) and STATA/SE 10 (20). PLINK was used to determine number of CNVs and total size of CNVs for each individual. In addition to analyzing the effect of all CNVs, we also separately examined the effects of common CNVs (found in more than 10% of individuals) and rare CNVs (found in less than 10% of individuals). Analyses were undertaken to investigate the effects of harbouring any CNVs, and more specifically for the effect of deletion or duplication CNVs. CNVs were further annotated as to whether they covering gene-coding regions (genic) or exon-coding regions (exonic) as defined by RefSeq gene annotation coordinates obtainable from the UCSC genome browser (http://genome.ucsc.edu). For information about the number of individuals with a CNV in each of the categories examined, see supplementary materials.

CNV data were analysed using four linear regressions: (1) the entire sample, (2) only those individuals taking a SSRI, (3) only those individuals taking a NRI, (4) differential response to treatment with either a SSRI or NRI (CNV by drug interaction). Analyses were co-varied for the standard deviation of the log relative ratio and four principal components from the final

iteration of the EIGENSTRAT analysis of LD-pruned genetic data to minimise the influence of population stratification (1).

Analyses were also performed within each contributing sample and meta-analysed (see Supplementary materials).

Power Analysis

We aimed to determine if presence, number or burden of CNVs would predict response to antidepressant treatment in a clinically significant way. Simulations based on large antidepressant treatment trials have shown that a prediction is usually judged to be clinically significant if it explains at least 6.33% of the variance in the response outcome (21). Using the pwr package (Power analysis functions along the lines of Cohen (22)) in R (23), we calculated the power of our four analyses (whole sample, serotonergic, noradrenergic, and gene by drug interaction). All of our analyses had power (greater than 90%) to detect a clinically significant finding at the alpha level of $p<0.05$. All analyses had an adequate statistical power (>80%) to detect even a signal that explains only half of what would be clinically significant prediction.

Results

In the combined sample, 1,565 individuals passed quality control for both the whole genome association study and the CNV calls.

We found no association between presence of any CNV, total number of CNVs or global CNV burden and response to any antidepressant, serotonergic antidepressants, noradrenergic antidepressants or differential response to serotonergic and noradrenergic antidepressants (Table 1). There was no relationship with rare or common CNVs or deletions or duplications.

We carried out additional analyses, restricted to CNVs which encompassed gene coding regions (genic) or exon coding regions (exonic), but we found no significant association

between presence of CNV, global number of CNVs or global CNV burden and antidepressant response, response to serotonergic antidepressants, response to noradrenergic antidepressants or differential response to serotonergic and noradrenergic antidepressants (Tables 2 and 3). Furthermore, there was no association with genic or exonic rare or common CNVs or deletions or duplications.

Discussion

CNVs have been implicated in the aetiology of several psychiatric disorders including major depression where we have previously reported an overall excess of deletions affecting exons in cases compared with controls (Rucker paper). It is reasonable to hypothesise that CNVs might also influence the form or course of the illness and this is the first investigation into the relationship between antidepressant response and CNVs. We took a comprehensive approach to explore the role of CNVs in response to antidepressant treatment by assessing both global number and burden of CNVs and considering possibly specific roles of duplications, deletions, rare, common, genic and exonic CNVs. However in each of these analyses, we found no association between CNVs and antidepressant response.

Our negative results for the role of CNVs and antidepressant response add to the growing literature of negative genome wide association studies (GWAS) for antidepressant response (1-5). By contrast, analysis of GWAS data on response to antidepressants provides perhaps the best evidence to date that it is a heritable trait (Tansey in press BP paper). While there are still other forms of genetic variation that have yet to be investigated, such as rare or personal single nucleotide mutations, it seems unlikely that any single genetic variation or simple combination of variants will be clinically useful in the personalising antidepressant medication. What is emerging instead is that antidepressant response is a complex polygenic (and likely polyenvironmental) quantitative trait. It remains to be seen whether more complex

combinatorial approaches, based for example on machine learning, can help tease out key genetic elements.

Our study has several limitations which should be taken into consideration when interpreting these results. Our analysis classifies antidepressants into mechanism of action (serotonergic versus noradrenergic) and cannot inform about the role of CNVs for a specific drug. Furthermore, our analysis focused on global measures of CNVs rather than specific deletions or duplication events which may affect an individual's response to treatment. We obtained our large sample by bringing together numerous different studies which differ by rating scale used and method to recruit subjects. We took these steps as we are interested in predictors of antidepressant response which generalize to most individuals with MDD. Furthermore, our studies focus only on individuals of Caucasian/European ancestry and monoaminergic antidepressants. Results in other population and/or in drugs whose mechanism of action is non-monoaminergic may yield different results.

Conclusions

We have investigated for the first time the role of CNVs in response to treatment with antidepressants. We find no association between antidepressant response for global number or burden of CNVs. The growing literature of negative genetic associations for antidepressant response implies that use of some types of genetic information to personalise treatment of MDD is not likely in the near future. Future large studies investigating known functional variants not adequately captured by this type of analysis and various clinical and biological features, such as transcriptomics and/or epigenomics, are needed along with complex multivariate prediction algorithms to personalise treatment of MDD with antidepressants.

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Author Contribution

Tansey carried out the data analysis. Rucker called the CNVs using Penn and QuantiSNP. Tansey and Uher wrote the report. Guipponi undertook the genotyping. C.M.Lewis supervised the statistical analyses and critically revised the report. Perroud, Bondolfi,

Domenici, Evans, Hall, Hauser, Henigsberg, Hu, Jerman, Maier, Mors, O'Donovan, Peters, Placentino, Rietschel, Souery,Aitchison, Craig, Farmer, Malafosse, and G. Lewiscontributed to study design, recruited participants, processed samples and aided in preparation of the manuscript. Wendland, Bryan Stensbøl, Kapur, McGuffin, and Uher conceived the study and critically revised the report. McGuffin and Uher oversaw all aspects of the study. Tansey and Uher had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.All authors approved the final version of the manuscript.

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Table 1: NEWMEDS CNV results for ALL CNVs. Regression coefficient is standardized and can be interpreted as a measure of effect size.. Positive values of regression coefficient mean that carriers of more minor alleles had better treatment outcome. Negative values of regression coefficient mean that carriers of more minor alleles had worse outcomes.

All CNVs	Whole Sample Analysis (n=1,565)		Serotonergic Analysis (n=1,046)		Noradrenergic Analysis (n=519)		Gene by Drug Interaction (n=1,565)	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value
Any CNV	-0.015 (0.058)	0.799	-0.0001 (0.071)	0.999	-0.034 (0.104)	0.742	-0.022 (0.126)	0.863
Number of CNVs	-0.012 (0.021)	0.572	-0.022 (0.025)	0.384	0.022 (0.037)	0.557	0.045 (0.045)	0.315
Burden of CNVs	0.00002 (0.00005)	0.739	-0.00002 (0.00007)	0.786	0.00005 (0.00006)	0.400	0.00008 (0.0001)	0.382
Any deletion CNV	-0.082 (0.051)	0.108	-0.108 (0.062)	0.085	-0.013 (0.090)	0.884	0.100 (0.109)	0.358
Number of deletion CNVs	-0.043 (0.036)	0.232	-0.045 (0.044)	0.299	-0.025 (0.062)	0.686	0.022 (0.076)	0.774
Burden of deletion CNVs	0.000009 (0.00007)	0.889	-0.0002 (0.0001)	0.286	0.00006 (0.00008)	0.425	0.0002 (0.0002)	0.161
Any duplication CNV	0.038 (0.051)	0.461	0.041 (0.062)	0.514	0.044 (0.090)	0.623	0.013 (0.109)	0.908
Number of duplication CNVs	0.004 (0.025)	0.870	-0.010 (0.031)	0.739	0.042 (0.043)	0.329	0.054 (0.054)	0.313
Burden of duplication CNVs	0.00002 (0.00008)	0.743	0.00002 (0.00008)	0.766	0.00004 (0.0001)	0.759	0.00002 (0.0001)	0.890
Any rare CNV	-0.012 (0.050)	0.812	-0.043 (0.061)	0.482	0.064 (0.087)	0.463	0.119 (0.106)	0.263
Number of rare CNVs	-0.008 (0.028)	0.789	-0.034 (0.035)	0.333	0.058 (0.049)	0.241	0.096 (0.060)	0.110
Burden of rare CNVs	0.00003 (0.00005)	0.577	-0.00001 (0.00008)	0.856	0.00007 (0.00007)	0.318	0.00009 (0.0001)	0.367
Any rare deletion CNV	-0.069 (0.055)	0.209	-0.103 (0.067)	0.124	0.016 (0.096)	0.870	0.121 (0.116)	0.297
Number of rare deletion CNVs	-0.033 (0.042)	0.436	-0.047 (0.052)	0.365	0.007 (0.071)	0.925	0.053 (0.879)	0.548
Burden of rare deletion CNVs	0.00002 (0.00007)	0.742	-0.0001 (0.0002)	0.363	0.00007 (0.00008)	0.382	0.0002 (0.0002)	0.207
Any rare duplication CNV	0.020	0.707	-0.021	0.741	0.114	0.207	0.152	0.166

	(0.052)		(0.064)		(0.090)		(0.110)	
Number of rare duplication CNVs	0.015 (0.036)	0.664	-0.017 (0.043)	0.699	0.091 (0.062)	0.140	0.115 (0.076)	0.128
Burden of rare duplication CNVs	0.00003 (0.00007)	0.663	0.00003 (0.00009)	0.744	0.00005 (0.0001)	0.686	0.00004 (0.0002)	0.823
Any common CNV	-0.003 (0.050)	0.950	0.031 (0.061)	0.610	-0.069 (0.087)	0.429	-0.088 (0.106)	0.405
Number of common CNVs	-0.011 (0.032)	0.721	-0.004 (0.039)	0.927	-0.016 (0.053)	0.771	-0.016 (0.066)	0.808
Burden of common CNVs	-0.00008 (0.0002)	0.607	-0.00004 (0.0002)	0.824	-0.0001 (0.0003)	0.707	-0.00007 (0.0003)	0.839
Any common deletion CNV	-0.048 (0.072)	0.505	-0.005 (0.087)	0.950	-0.136 (0.128)	0.289	-0.124 (0.156)	0.428
Number of common deletion CNVs	-0.035 (0.064)	0.583	-0.013 (0.078)	0.870	-0.075 (0.116)	0.518	-0.059 (0.140)	0.671
Burden of common deletion CNVs	-0.0002 (0.0003)	0.529	-0.0002 (0.0004)	0.657	-0.0002 (0.0005)	0.770	0.00004 (0.0006)	0.955
Any common duplication CNV	0.013 (0.051)	0.799	0.025 (0.062)	0.694	-0.006 (0.088)	0.941	-0.025 (0.108)	0.820
Number of common duplication CNVs	-0.008 (0.038)	0.840	-0.003 (0.048)	0.952	-0.005 (0.062)	0.938	-0.007 (0.079)	0.929
Burden of common duplication CNVs	-0.00004 (0.0002)	0.833	0.000002 (0.0003)	0.995	-0.00007 (0.0003)	0.842	-0.00008 (0.0004)	0.844

Table 2: NEWMEDS CNV results for CNVs encompassing regions annotated to harbour genes. Regression coefficient is standardized and can be interpreted as a measure of effect size.. Positive values of regression coefficient mean that carriers of more minor alleles had better treatment outcome. Negative values of regression coefficient mean that carriers of more minor alleles had worse outcomes.

GENIC CNVs	Whole Sample Analysis (n=1,565)		Serotonergic Analysis (n=1,046)		Noradrenergic Analysis (n=519)		Gene by Drug Interaction (n=1,565)	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value
Any CNV	-0.042 (0.051)	0.415	-0.049 (0.063)	0.433	-0.012 (0.091)	0.895	0.049 (0.110)	0.658
Number of CNVs	-0.008 (0.025)	0.750	-0.016 (0.030)	0.606	0.018 (0.043)	0.674	0.041 (0.052)	0.438
Burden of CNVs	0.00003 (0.00005)	0.617	0.00001 (0.00009)	0.898	0.00004 (0.00007)	0.519	0.00005 (0.0001)	0.652
Any deletion CNV	-0.082 (0.060)	0.172	-0.068 (0.073)	0.354	-0.098 (0.105)	0.350	-0.002 (0.128)	0.986
Number of deletion CNVs	-0.085 (0.048)	0.080	-0.066 (0.060)	0.275	-0.108 (0.082)	0.188	-0.023 (0.102)	0.821
Burden of deletion CNVs	0.0000005 (0.00007)	0.994	-0.0001 (0.0002)	0.382	0.00004 (0.00008)	0.648	0.0002 (0.0002)	0.272
Any duplication CNV	0.019 (0.050)	0.701	-0.008 (0.061)	0.893	0.091 (0.087)	0.298	0.101 (0.106)	0.339
Number of duplication CNVs	0.019 (0.029)	0.506	0.001 (0.035)	0.972	0.064 (0.050)	0.197	0.065 (0.061)	0.284
Burden of duplication CNVs	0.00005 (0.00007)	0.482	0.00005 (0.00009)	0.545	0.00006 (0.0001)	0.624	0.00002 (0.0002)	0.898
Any rare CNV	0.006 (0.052)	0.905	0.001 (0.063)	0.985	0.031 (0.089)	0.729	0.044 (0.109)	0.689
Number of rare CNVs	0.005 (0.034)	0.877	-0.009 (0.043)	0.834	0.044 (0.058)	0.440	0.067 (0.072)	0.350
Burden of rare CNVs	0.00004 (0.00005)	0.446	0.00003 (0.00009)	0.717	0.00005 (0.00007)	0.452	0.00004 (0.0001)	0.748
Any rare deletion CNV	-0.057 (0.067)	0.390	-0.033 (0.081)	0.681	-0.105 (0.117)	0.371	-0.044 (0.143)	0.760
Number of rare deletion CNVs	-0.068 (0.055)	0.217	-0.040 (0.069)	0.557	-0.112 (0.091)	0.222	-0.051 (0.115)	0.658
Burden of rare deletion CNVs	0.00001 (0.00007)	0.0858	-0.0001 (0.0002)	0.572	0.00004 (0.00008)	0.649	0.0002 (0.0002)	0.434

Any rare duplication CNV	0.038 (0.055)	0.490	-0.011 (0.068)	0.866	0.153 (0.093)	0.103	0.177 (0.115)	0.126
Number of rare duplication CNVs	0.042 (0.041)	0.301	0.009 (0.050)	0.861	0.123 (0.071)	0.081	0.122 (0.087)	0.161
Burden of rare duplication CNVs	0.00006 (0.00008)	0.411	0.00007 (0.0001)	0.489	0.00008 (0.001)	0.577	0.00002 (0.0002)	0.895
Any common CNV	-0.026 (0.050)	0.601	-0.041 (0.062)	0.502	0.009 (0.088)	0.915	0.062 (0.107)	0.563
Number of common CNVs	-0.025 (0.038)	0.510	-0.028 (0.048)	0.562	-0.013 (0.063)	0.831	0.014 (0.079)	0.859
Burden of common CNVs	-0.0001 (0.0002)	0.476	-0.0001 (0.0002)	0.582	-0.00009 (0.0003)	0.750	0.00003 (0.0004)	0.928
Any common deletion CNV	-0.139 (0.103)	0.177	-0.149 (0.128)	0.244	-0.083 (0.173)	0.631	0.079 (0.215)	0.712
Number of common deletion CNVs	-0.135 (0.100)	0.175	-0.143 (0.122)	0.242	-0.083 (0173)	0.631	0.072 (0.211)	0.734
Burden of common deletion CNVs	-0.0003 (0.0004)	0.365	-0.0005 (0.0005)	0.326	0.00003 (0.0006)	0.966	0.0005 (0.0008)	0.500
Any common duplication CNV	0.005 (0.053)	0.920	-0.003 (0.064)	0.968	0.018 (0.092)	0.843	0.030 (0.112)	0.787
Number of common duplication CNVs	-0.003 (0.042)	0.945	-0.006 (0.053)	0.913	0.006 (0.069)	0.926	0.011 (0.087)	0.896
Burden of common duplication CNVs	-0.00003 (0.0002)	0.883	-0.00002 (0.0003)	0.946	-0.00003 (0.0004)	0.931	-0.000009 (0.0005)	0.985

Table 3: NEWMEDS CNV results for CNVs annotated to encompass exonic regions of genes. Regression coefficient is standardized and can be interpreted as a measure of effect size.. Positive values of regression coefficient mean that carriers of more minor alleles had better treatment outcome. Negative values of regression coefficient mean that carriers of more minor alleles had worse outcomes.

EXONIC CNVs	Whole Sample Analysis (n=1,565)		Serotonergic Analysis (n=1,046)		Noradrenergic Analysis (n=519)		Gene by Drug Interaction (n=1,565)	
	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	p-value	Coefficient (SE)	P-value
Any CNV	-0.028 (0.051)	0.591	-0.038 (0.062)	0.546	0.008 (0.090)	0.929	0.054 (0.109)	0.623
Number of CNVs	-0.002 (0.025)	0.943	-0.014 (0.031)	0.656	0.032 (0.043)	0.458	0.053 (0.053)	0.322
Burden of CNVs	0.00003 (0.00005)	0.547	0.00001 (0.00008)	0.855	0.00005 (0.00007)	0.466	0.00005 (0.0001)	0.644
Any deletion CNV	-0.064 (0.061)	0.300	-0.070 (0.075)	0.346	-0.036 (0.108)	0.737	0.057 (0.131)	0.661
Number of deletion CNVs	-0.073 (0.051)	0.148	-0.067 (0.063)	0.285	-0.075 (0.086)	0.387	0.012 (0.107)	0.911
Burden of deletion CNVs	0.000008 (0.00007)	0.916	-0.0001 (0.0002)	0.404	0.00004 (0.00008)	0.589	0.0002 (0.0002)	0.274
Any duplication CNV	0.019 (0.050)	0.701	-0.008 (0.061)	0.893	0.091 (0.087)	0.298	0.102 (0.106)	0.339
Number of duplication CNVs	0.021 (0.029)	0.460	0.003 (0.035)	0.930	0.067 (0.050)	0.178	0.066 (0.061)	0.276
Burden of duplication CNVs	0.00005 (0.00007)	0.457	0.00006 (0.00008)	0.521	0.00007 (0.0001)	0.608	0.00002 (0.0002)	0.898
Any rare CNV	0.025 (0.052)	0.630	0.010 (0.064)	0.878	0.068 (0.090)	0.446	0.073 (0.110)	0.508
Number of rare CNVs	0.018 (0.035)	0.611	-0.004 (0.044)	0.918	0.071 (0.059)	0.228	0.089 (0.073)	0.222
Burden of rare CNVs	0.00005 (0.00005)	0.385	0.00004 (0.00009)	0.672	0.00006 (0.00007)	0.401	0.00004 (0.0001)	0.744
Any rare deletion CNV	-0.027 (0.069)	0.702	-0.030 (0.084)	0.723	-0.021 (0.125)	0.869	0.037 (0.150)	0.806
Number of rare deletion CNVs	-0.050 (0.058)	0.389	-0.039 (0.072)	0.592	-0.068 (0.097)	0.481	-0.008 (0.121)	0.945
Burden of rare deletion CNVs	0.00002 (0.00007)	0.780	-0.00009 (0.0002)	0.603	0.00004 (0.00008)	0.589	0.0002 (0.0002)	0.442

Any rare duplication CNV	0.041 (0.055)	0.451	-0.011 (0.068)	0.866	0.163 (0.094)	0.082	0.187 (0.115)	0.105
Number of rare duplication CNVs	0.047 (0.041)	0.253	0.013 (0.051)	0.801	0.129 (0.071)	0.068	0.124 (0.087)	0.154
Burden of rare duplication CNVs	0.00007 (0.00009)	0.386	0.00007 (0.0001)	0.464	0.00008 (0.0001)	0.561	0.00002 (0.0002)	0.897
Any common CNV	-0.026 (0.050)	0.601	-0.041 (0.062)	0.502	0.009 (0.088)	0.915	0.062 (0.107)	0.563
Number of common CNVs	-0.025 (0.038)	0.510	-0.028 (0.048)	0.562	-0.013 (0.063)	0.831	0.014 (0.079)	0.859
Burden of common CNVs	-0.0001 (0.0002)	0.476	-0.0001 (0.0002)	0.582	-0.00009 (0.0003)	0.750	0.00003 (0.0004)	0.928
Any common deletion CNV	-0.139 (0.103)	0.177	-0.149 (0.128)	0.244	-0.083 (0.173)	0.631	0.079 (0.215)	0.712
Number of common deletion CNVs	-0.135 (0.100)	0.175	-0.143 (0.122)	0.242	-0.083 (0.173)	0.631	0.072 (0.211)	0.734
Burden of common deletion CNVs	-0.0004 (0.0004)	0.365	-0.0005 (0.0005)	0.326	0.00003 (0.0006)	0.966	0.0005 (0.0008)	0.500
Any common duplication CNV	0.005 (0.053)	0.920	-0.003 (0.064)	0.968	0.018 (0.092)	0.842	0.030 (0.112)	0.787
Number of common duplication CNVs	-0.003 (0.042)	0.945	-0.006 (0.053)	0.913	0.006 (0.069)	0.926	0.011 (0.087)	0.896
Burden of common duplication CNVs	-0.00003 (0.0002)	0.883	-0.00002 (0.0003)	0.946	-0.00003 (0.0004)	0.931	-0.000009 (0.0005)	0.985